Effect of eight weeks' training with or without EMG-biofeedback, on shoulder pain and function in patients with subacromial impingement
an assessor-blinded randomised controlled trial
Juul-Kristensen, Birgit; Larsen, Camilla Marie; Eshoj, Henrik; Clemmensen, Trine Holt; Hansen, Anders; Jensen, Peter Bo; Boyle, Eleanor; Søgaard, Karen

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Statistical Analysis plan

**Effect of eight weeks’ training with or without EMG-biofeedback, on pain and function in patients with subacromial impingement - an assessor-blinded randomised controlled clinical trial**

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'Statistical Analysis Plan (SAP): Effect of eight weeks’ training with or without EMG-biofeedback, on shoulder pain and function in patients with subacromial impingement - an assessor-blinded randomised controlled trial.'
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1. STUDY SYNOPSIS

Subacromial impingement syndrome (SIS) is a common shoulder disorder in primary sector (Luime, 2004). It is characterized by shoulder pain exacerbated by overhead activities which may be due to compression of the subacromial structures such as rotator cuff muscle tendons (Neer, 1972, Fu et al., 1991). SIS may be caused by inappropriate scapulo-humeral movement due to neuromuscular imbalance of the scapular muscles (Page, 2011) that may be caused by shoulder pain and impaired shoulder function. Consequently, current treatment guidelines for patients with SIS focus on restoration of the neuromuscular system. Previously, EMG biofeedback has shown to be a promising clinical tool for teaching individuals with or without shoulder pain a functional healthy muscle activity pattern (Holtermann et al., 2009, Holtermann et al., 2010, Huang et al., 2013, Larsen CM et al., 2013, Larsen et al., 2014). However, no randomised controlled trial has yet studied the effect of using such EMG biofeedback program in combination with neuromuscular training of the scapular muscles versus using a neuromuscular training programme only.

Ethical Trial registration from the Committee on Biomedical Research Ethics for the Region of Southern Denmark, Denmark: Project ID S-20090090. Clinical Trial: 03/11/2017, no: 34384.

2. PURPOSE OF ANALYSIS

This study aimed to evaluate the effect of eight weeks of EMG-biofeedback supervised neuromuscular shoulder exercise (intervention group) versus only neuromuscular shoulder exercise (control group) in patients with subacromial impingement as measured by shoulder pain, function and muscle activity.

3. STUDY OBJECTIVES AND HYPOTHESIS

This study tests the hypothesis that patients receiving eight weeks of neuromuscular shoulder exercise programme with EMG-biofeedback (BIONEX) will be superior in reducing short term shoulder pain, function and EMG changes of shoulder-muscles compared with patients treated with eight weeks of neuromuscular shoulder exercise programme without EMG-biofeedback (NEX).

4. STUDY METHODS

4.1. Design

This trial was a randomised (1:1), assessor-blinded, controlled clinical superiority trial with a paralleled group design investigating the efficacy of BIONEX versus the same exercise programme without receiving EMG biofeedback (NEX) in patients with subacromial impingement (see flowchart, Figure 1). Patient recruitment was conducted from 1/4-2009
to 11/7 2012 in The Region of Southern Denmark. Participants were recruited from specialized clinics in Odense, the rehabilitation department in the municipality of Odense, sports clubs in Odense and social media.

4.2. Study population

**Population:** Participants included were women and men within the age of 19-67 years. Participants were randomised to BIONEX or NEX provided they fulfilled the below listed criteria:

**Inclusion criteria**

- age between 19-67 years
- at least 30 days of pain/discomfort in the shoulder/neck region within the past year (Juul-Kristensen et al., 2006)
- at least two positive clinical impingement tests based on the Jobe, Neer, Hawkins and Apprehension tests (Cools et al., 2008, Vind et al., 2011).

**Exclusion criteria**

- ≥ 8 in shoulder pain/discomfort - measured with Numeric Pain Rating Scale from 0-10 (NPRS) - throughout the past 24 hours (on the test day),
- more than three body regions with pain or trouble for a minimum of 30 days or more of trouble during the past 12 months,
- history of severe shoulder-neck pathology/trauma and/or orthopaedic surgery and/or injections in the affected shoulder within the past three months,
- pregnancy,
- any documented life threatening diseases, cardiovascular diseases, rheumatoid arthritis, generalized pain, adverse psychosocial conditions as well as positive signs for cervical radiculopathy, i.e. Spurling A test, Involved Cervical Rotation test (less than 60 degrees), Neck Distraction test (Wainner et al., 2003).

4.3. Interventions

Based on best evidence from previous studies on muscular imbalance between the upper trapezius (UT), the lower trapezius (LT) and the serratus anterior (SA) muscles a standardised intervention program was developed consisting of exercises for activating LT and SA (Arlotta et al., 2011, Maenhout et al., 2009, Phadke et al., 2009, Reinold et al., 2009, Feleus et al., 2009, Kibler et al., 2008, Kinney et al., 2008, Cools et al., 2007, Hardwick et al.,
2006, McClure et al., 2004, Ekstrom et al., 2003, Decker et al., 1999, Mottram, 1997, Townsend et al., 1991). The only difference between the two intervention groups was that once a week the BIONEX group received a supervised EMG-biofeedback exercise session on muscle activity in relation to the exercise instructions and the NEX group only received exercise instructions (same exercises without supervised EMG-biofeedback). Thus both groups (the BIONEX and the NEX group) received the following supervised exercise program once a week:

- The exercise program was divided into two phases consisting of 2-3 exercises with 2 x 10 repetitions to be performed once a day (non-supervised at home).

In phase one, from week 1 to 3, the focus was on learning scapula setting, and re-learning of activation of LT & SA.

In the second phase, from week 4 to 8 aspects of the previous exercises were applied in more functional load progressive exercises.

Also, stretching exercises and ergonomic instructions were given (Ludewig and Reynolds, 2009, Borstad and Ludewig, 2005). A detailed description of the exercise protocol will be added in an appendix to the final article describing the effect of eight weeks of training with or without EMG-biofeedback, on pain and muscle function in patients with subacromial impingement - an assessor-blinded randomised controlled clinical trial.

5. EFFICACY

Primary self-reported endpoint was at eight weeks follow-up. Secondary self-reported and measured endpoints were also performed at eight weeks follow-up. In addition, self-reported secondary endpoints were recorded at baseline and once every week until the eight-week follow-up after baseline.

6. OUTCOME VARIABLES

6.1. Primary outcome

The primary outcome was shoulder pain during the past seven days using the Numeric Pain Rating Scale (NPRS). The NPRS is a scale with 11 steps from 0-10 (0=no pain, 10=worst imaginable pain) (Downie et al., 1978).

6.2 Key secondary outcomes

Key secondary patient reported outcomes were obtained from all participants at baseline and eight weeks follow-up.
Furthermore, participants were asked to register in a diary their daily shoulder pain level throughout the eight weeks of home exercise.

Also, key secondary objective physical test outcomes were obtained from all participants at baseline and the eight weeks follow-up only.

In general, all of the key secondary outcomes are used to interpret the results from the primary outcome.

6.2.1 Patient reported

-NPRS was used according to the question “actual shoulder pain level” and “shoulder pain level within the previous 24 hours”,

-Disability of the Arm, Shoulder and Hand questionnaire (DASH), a 30 item scale designed to describe experienced disability with upper-limb disorders, and to monitor changes in symptoms and function over time. Each question/item is rated on a five-point Likert scale, scoring from 1-5, (1= good function and/or no pain, 5= poor function and/or worst possible pain) (Gummesson et al., 2003),

-Sub dimensions of the DASH questionnaire, called Work and Sports/Performing Arts activities, each with 4 items rated on a five-point Likert scale, as in the DASH questionnaire described above,

-Oxford Shoulder Score (OSS), measures shoulder function using a five-point Liker scale for each question (4=good function, 0=poor function) (Frich et al., 2011),

-Average weekly shoulder pain during the eight weeks of shoulder neuromuscular intervention, as measured with NPRS.

6.2.2. Objective physical tests

-Surface electromyography (sEMG) signals measuring shoulder muscle activity were obtained from three scapular muscles: Upper Trapezius (UT), Lower Trapezius (LT) and SA (SA) during standardised bilateral voluntary movement tasks (arm elevation and lowering), with each direction (up, down) repeated five times, at three different loads (no-load, 1 kg, 3 kg).

The following EMG variables were calculated:

- mean relative muscle activity (percentage of maximal voluntary electric activity, %MVE during arm elevation and arm lowering),

- muscle activation ratios between the muscles during arm elevation and arm lowering (UT/LT and UT/SA),

- muscle onset time (UT-SA, LT-SA, UT-LT).
6.3 Demographic data and compliance

All participants were asked to answer a number of questions collected at baseline and at the eight weeks follow up, including age, height, weight, educational level, work status, etc.

The diary used for home exercises (rating of daily pain level) also contained exercise notations on the daily training and was thus used to measure the compliance rate in relation to the participation rate in execution of the home exercises. Further, compliance with the supervised EMG-biofeedback neuromuscular shoulder exercise programme (intervention group) was registered by the treating physiotherapist as the number of supervised sessions attended by the patient.

For the treatment-related variables in the BIONEX group compliance is classified in accordance with the following criteria:

- Satisfactory (as defined per protocol) compliance for the patients is 75% participation (at least six supervised sessions out of eight possible sessions), and
- Completion of at least 75% of the scheduled home-based exercises (one exercise and one stretching exercise per day) as registered in the training diary.

Compliance to the NEX program (control) was defined as completion of at least two thirds (75%) of the scheduled home-based exercises as registered by use of the training diary.

7. RANDOMISATION, ALLOCATION AND BLINDING PROCEDURES

Following baseline assessment participants were randomly assigned to either of the two exercise groups (BIONEX and NEX) using a blocked randomisation method (Kang et al., 2008, Altman and Bland, 1999). The block size was chosen to be six (three EMG and three no-EMG) and six folders in all were made (=36 possible participants), but one folder had to be emptied before starting on a new.

A list of random numbers (1:1) was prepared prior to starting the study and was concealed in sequentially numbered and opaque envelopes, stating which group every single individual was allocated to. After baseline measurements the randomization envelope was opened by the patient, who was told not to disclose group assignment. After having read the letter the envelope, including the randomisation letter, was closed by the patient and stored in a locker close to where the supervised training session was performed. The outcome assessors then forwarded name and telephone number to the treating physiotherapist who contacted the patient for scheduling an appointment for the first exercise instruction. At the first visit, the treating physiotherapist opened the envelope and the supervised session could begin (with or without EMG biofeedback).

Outcome assessors performing all outcome measurements were kept blinded to treatment allocation and were also not involved in the treatment of patients (Flowchart, Figure 1). The treating physiotherapists did not have access to the responses of the baseline outcome measurements.
Blinding of treatment allocation for patients and physiotherapists were not possible due to the design. To retain the blinding of the outcome assessors, patients were encouraged not to reveal their treatment assignment at the eight-week follow-up. Raw data was sent to an impartial data engineer/data analyst before returning later for further statistical analysis.

All steps to avoid motivational issues, from either investigator or/and test-subject was considered in order to avoid affecting the internal validity (Bowling, 2014).

Also, the statistical analysis plan will be carried through blinded according to group allocation, and results will be interpreted in an author consensus statement prior to disclosing/revealing group allocation on the basis of a blinded review of the data from the primary endpoint (changes from treatment A compared to changes from treatment B), assuming that treatment A is the active treatment (BIONEX), and the other assuming that treatment B is the active treatment (BIONEX). Not until a signed consent from all of the authors of this trial (identical to the authors of this SAP) has been obtained, agreeing on one interpretation of the results only, the randomization code will be broken. This is done to reduce bias in the interpretation of the current findings. On agreement, all members of the author group will approve and sign the interpretations before any publication procedures are initiated (Jarvinen et al., 2014).

8. SAMPLE SIZE

This study was designed as an exploratory superiority trial with two groups (BIONEX and NEX) using the patient reported NPRS for pain intensity, determined to be clinically relevant for musculoskeletal pain as primary outcome. The power and sample size calculation was based on difference in NPRS change score between the two groups from baseline to the eight weeks follow up.

It was expected that the group allocated to BIONEX improved two points more than the group allocated to NEX based on the primary outcome NPRS at the end point of eight weeks (Salaffi et al., 2004). Based on this a sample size of 10 subjects per group was required to detect a statistical significant difference of two NPRS points with a standard deviation of 1.5, at a power of 80%, and an alpha level of 0.05, including possible barriers, non-compliant patients and patients who were lost-to-follow-up.

Due to the importance of the EMG variable in this design we also wanted to ensure sufficient power for detecting between-group differences in EMG variables. Therefore, a power calculation with 80% power, an alpha level of 0.05, a standard deviation of 42% in MVE and a 25% between-group difference in changed MVE values, revealed a minimal sample size of 22 subjects per group (Ludewig and Cook, 2000, Larsen et al., 2013). However, we included a minimum of 50 subjects to be able to account for missing data. Though, for practical and logistical reasons, enrolment of patients ended in 3/5 2012.

9. STATISTICAL ANALYSIS
9.1 Primary endpoint

The between-group difference in change in the NPRS score in shoulder pain during the past seven days from baseline to eight weeks follow-up will be the primary endpoint.

9.2 Secondary endpoints

The key secondary outcomes (patient reported) will be analysed as the difference between study groups in the change from baseline to the eight weeks follow-up. Furthermore, group differences in changed mean weekly shoulder pain (derived from diary ratings of daily pain) throughout the eight weeks of home exercise will be analysed.

The key secondary objective measurements (sEMG) will be analysed as the difference between study groups in the change from baseline to the eight weeks follow-up.

All analyses will follow the intention-to-treat principle; i.e., all participants in the trial will be included in the analysis according to the group to which they were randomised, regardless of drop out/any departures from allocated treatment. Missing data will be replaced using a non-responder imputation, in which the baseline value is carried forward (Little et al., 2012). The rational behind this type of analysis builds on the assumption that those who dropped out returned to their baseline NPRS score (White et al., 2011).

For sensitivity and exploratory purposes also a per-protocol analysis, including those with good compliance (as previously described) with the protocol (incl. outcome assessments available after eight weeks) will be performed.

A linear regression model will be used to analyse mean changes in continuous end points (NPRS, DASH, OSS, %MVE UT, %MVE LT, %MVE SA, UT/LT ratio, UT/SA ratio, onset times UT-SA, LT-SA, UT-LT from baseline to eight weeks follow-up. For each of these variables (used as dependent variable) the model will include exposure (BIONEX, NEX), sex, baseline variable of the relevant variable, BMI and age.

A multilevel linear mixed model will be used to analyse the EMG data. The exposure, sex, BMI, age and load will be entered into the model. The interactions between time, exposure and load, time and load, in addition to exposure and load will be tested.

In addition, for the NPRS values as measured once a week (0-8) during the eight weeks of exercise (BIONEX or NEX) for both groups data will be analyzed by repeated measures from the multilevel linear mixed model, adjusted for baseline NPRS scores.

An alpha-level of 0.05 will be considered as being statistically significant (p < 0.05, two-sided). Finally, results will be expressed as the difference between group-means with 95% Confidence Intervals and the associated p-values. Statistical analyses will be performed in Statistical Package for the Social Sciences (SPSS, IBM, Armonk NY, USA, version 24.0).

10. IMPLEMENTATION OF ANALYSIS PLAN
A statistical advisor and epidemiologist (EB) will perform the analysis on primary outcome and principal investigators will perform analyses on secondary outcomes.

The implementation of the SAP for the BIONEX study will follow the procedure below:

1. A database model will be lined up in collaboration between the epidemiologist (EB) and principal investigators.

2. A secretary outside the study (AMR) will code each treatment arm into 'group treatment A' and 'group treatment B', thus leaving all others blinded to treatment allocation during analysis.

3. Blinded data of primary outcome will be delivered to the epidemiologist according to the database model.

4. Primary, secondary, sensitivity and exploratory analyses will be conducted blinded from allocation to any of the two treatment arms.

Results of primary outcomes will be presented to the principal investigators and co-authors of the manuscript.
11. TABLE AND FIGURE LEGENDS

**Figure 1:** Flow of participants throughout the study

**Table 1:** Baseline demographics for patients with subacromial impingement allocated to the BIONEX vs. NEX groups. Estimates are reported for each group and the total with Mean ± SD, n (%).

**Figure 2:** Numeric Pain Rating Scale (NPRS) at baseline, and each week from week 1-8 after baseline for the BIONEX vs. NEX Groups among patients with subacromial impingement. Data are derived from repeated-measures Linear Mixed model and adjusted for baseline NPRS scores. The graph illustrates the results from the Intention-To-Treat population. Data points represent least squares means and error bars indicate 95% CIs.

**Table 2:** Self-reported primary and secondary outcomes from baseline to eight-week follow-up for BIONEX vs. NEX groups among patients with subacromial impingement, Intention-To-Treat population.

**Table 3:** Objective outcomes (EMG-measurements -mean relative activity %MVE of UT, LT and SA, muscle activation ratios between the muscles (UT/LT and UT/SA), and onset time (UT-SA, LT-SA, UT-LT) from baseline to 8-week follow-up for BIONEX vs. NEX groups among patients with subacromial impingement.
Figure 1: Flowchart for the BIONEX study

Enrollment

Assessed for eligibility (n=104)

Excluded (n)
- Not meeting inclusion criteria (n=53)
  -- by telephone interview (n=32)
  -- by clinical examinations (n=21)
- Other reasons:
  -- EMG-recording errors (n=7)

Allocation (n=49)

Allocated to BIONEX (n=26)
  - Received allocated intervention (n=26)
  - Did not receive allocated intervention (n=)
    - Reason

Allocated to NEX (n=23)
  - Received allocated intervention (n=23)
  - Did not receive allocated intervention (n=)
    - Reason

8 weeks follow up

Lost to follow-up (n=3)
  Discontinued intervention due to:
  - Surgery (n)
  - Other reasons (n=3)

Lost to follow-up (n=2)
  Discontinued intervention due to:
  - Surgery (n)
  - Other reasons (n=2)

ITT analysis (n=49)

Analysed (n=25)
  - Excluded from analysis (n=)

Analysed (n=23)
  - Excluded from analysis (n=)

As observed analysis (n=44)

Analysed (n=23)
  - Excluded from analysis (n=)

Analysed (n=21)
  - Excluded from analysis (n=)

Per protocol analysis (n=)

Analysed (n=)
  - Excluded from analysis (n=)

Analysed (n=)
  - Excluded from analysis (n=)
Table 1. Baseline demographics for patients with subacromial impingement allocated to the BIONEX vs. NEX groups. Estimates are reported for each group and the total with Mean ± SD, n (%).

<table>
<thead>
<tr>
<th>Variables</th>
<th>BIONEX Group (n=..)</th>
<th>NEX Group (n=..)</th>
</tr>
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<tbody>
<tr>
<td>Gender (male (%))</td>
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<tr>
<td>Age (yrs) Mean (SD)</td>
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<td>Weight (kg) Mean (SD)</td>
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<td>Height (cm) Mean (SD)</td>
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<td>Educational level (n (%))</td>
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<tr>
<td>Academic</td>
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<td></td>
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<tr>
<td>White collar</td>
<td></td>
<td></td>
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<tr>
<td>Blue collar</td>
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<tr>
<td>Uneducated</td>
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Primary Outcome:
NPRS

Secondary Outcomes:
DASH total
DASH work
DASH Leisure time
OSS
EMG (%MVE)
UT elevation
UT lowering
LT elevation
LT lowering
SA elevation
SA lowering
EMG (ratio)
UT/LT elevation
UT/LT lowering
UT/SA elevation
UT/SA lowering
EMG (onset time, msec)
UT-SA elevation
UT-SA lowering
LT-SA elevation
LT-SA lowering
UT-LT elevation
UT-LT lowering

Abbreviations: NPRS Numeric Pain Rating Scale; DASH Disability of Arm Shoulder and Hand; OSS Oxford Shoulder Score; EMG Electromyography; %MVE percentage of Maximum Voluntary EMG; UT Upper Trapezius; LT Lower Trapezius; SA Serratus Anterior; Missing data =
**Figure 2:** Numeric Pain Rating Scale (NPRS) at baseline, week 1-8 for the BIONEX vs. NEX Groups among patients with subacromial impingement. Data are derived from repeated-measures Linear Mixed model and adjusted for baseline NPRS scores. The graph illustrates the results from the Intention-To-Treat population. Data points represent least squares means and error bars indicate 95% CIs.
Table 2: Self-reported primary and secondary outcomes from baseline to eight-week follow-up for BIONEX vs. NEX groups among patients with subacromial impingement, Intention-to-treat population.

<table>
<thead>
<tr>
<th></th>
<th>BIONEX group (n=)</th>
<th>NEX group (n=)</th>
<th>Between-Group difference (95% CI)</th>
<th>P Value</th>
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<tr>
<td><strong>Primary Outcome:</strong></td>
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<td>NPRS</td>
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<td><strong>Secondary Outcomes:</strong></td>
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<td>DASH total</td>
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**Abbreviations:** NPRS Numeric Pain Rating Scale; DASH Disability of Arm Shoulder and Hand; OSS Oxford Shoulder Score; Missing data =

Table 3. Objective outcomes (EMG-measurements -mean relative activity %MVE of UT, LT and SA, muscle activation ratios between the muscles (UT/LT and UT/SA), and onset time (UT-SA, LT-SA, UT-LT) from baseline to 8-week follow-up for BIONEX vs. NEX groups among patients with subacromial impingement, Intention-to-treat population.

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<th>Between-Group difference (95% CI)</th>
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<td><strong>Secondary Outcomes:</strong></td>
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<td>EMG (%MVE)</td>
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<td>EMG (ratio)</td>
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<td>LT-SA elevation</td>
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<td>UT-LT elevation</td>
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<td>UT-LT lowering</td>
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**Abbreviations:** EMG Electromyography; %MVE percentage of Maximum Voluntary EMG; UT Upper Trapezius; LT Lower Trapezius; SA Serratus Anterior; Missing data =
12. REFERENCES


